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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,088	07/13/2005	Jurgen Braunger	26797U	1055

34375 7590 04/02/2008

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112 South West Street
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EXAMINER	
PAGONAKIS, ANNA	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
04/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,088	BRAUNGER ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-42,44-49,62-70,75-82 and 84-85* is/are pending in the application.

4a) Of the above claim(s) *47-49,62-70,76, 79-82 and 85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-42,44-46,75,77,78 and 84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/10/2007, 4 sheets; 12/14/2005, 5 sheets; 10/17/2005, 6 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of roflumilast as the specific chemical compound and all trans retinoic acid as the specific differentiation inducing agent on the reply filed on 2/28/2008 is acknowledged. Because applicant did not distinctly and specifically point out supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 47-49, 76 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species, there being no allowable generic or linking claim.

Accordingly, no claims have been added, amended or cancelled.

Claims 39-42, 44-46, 75, 77-78 and 84 are presently under examination and are the subject of this Office Action.

Information Disclosure Statement

The information disclosure statements filed on 10/17/2005; 12/14/2005 and 4/10/2007 have been received. Documents with no year of publication provided were not considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 39, 41-46, 75, 77 and 84 rejected under 35 U.S.C. 103(a) as being unpatentable over Sigmund et al (Leukemia (2001), provided by Applicant) and Reid (Current Opinion in Investigational Drugs, provided by Applicant) and Sacchi et al. (Hematological 1997; 82: 106-121).

Sigmund et al. teach of a lymphocytic leukemia which rolipram a specific inhibitor of phosphodiesterase (PDE) type 4, the PDE predominantly expressed in B-CLL cells, has been shown to induce cAMP-dependent apoptosis in these cells (abstract). In lymphoid cells, cytolysis induced by phosphodiesterase (PDE) inhibition results from an increase in protein kinase A-mediated phosphorylation of uknown lymphoid target proteins which eventually induces apoptosis (page 1564, first column, last paragraph). Rolipram is also know to dose dependently increase intracellular cAMP levels leading to induction of apoptosis in resting B-CLL cells (page 1569, first column, last paragraph). In conclusion, since defective cell death mechanisms rather than dysregulation of cell cycle predominate in B-CLL, PDE4 inhibitors as pro-apoptotic agents may provide a therapeutic principle either as a single therapy in early-stage

patients or a combination therapy in advanced-stage patients with B-CLL (bridging pages 1569-1570).

Sigmund et al. does not teach the use of roflumilast as the PDE type 4 inhibitor, nor does it teach the use of all trans retinoic acid as a differentiation inducing agent.

Reid teaches that roflumilast is a nonselective PDE4 inhibitor which appears to be the major PDE isoenzyme involved in the regulation of cAMP-mediated functions in airway inflammatory and structural cells (introduction). Roflumilast is substantially more potent than rolipram (page 1165, synthesis and SAR, last 3 lines) and inhibit the functions of both immunocompetent and inflammatory cells to a greater level than rolipram (page 1168, second column, last paragraph).

Redi does not teach the use of roflumilast for the treatment of lymphoid diseases, not does it teach all trans retinoic acid as the differentiation inducing agent.

Sacchi et al teach that there is considerable evidence that retinoids have a potent antiproliferative effect, and may be effective in the treatment of a variety of human diseases including cancer (page 107, column 1, first 4 lines), further ATRA (all trans retinoic acid) has proven active against a range of malignancies in isolated tissue culture systems and in human clinical trials (page 109, column 1, under Metabolism). The therapeutic use of ATRA in acute promyelocytic leukemia (APL) was pioneered in the late eighties with results of 94 percent complete remissions (CR) using ATRA alone, generating tremendous interest in the clinical use of ATRA in APL (page 111, column 2, paragraph 3). Retinoids seem to have a preferential effect on patients with mature T-cell lymphoma. L-ATRA renders B-cell lymphoma lines more susceptible to apoptosis by down-regulating bcl-2 gene expression suggesting that L-ATRA

might be also useful for treating B-cell non-Hodgkin's lymphoma (page 115, column 1, first paragraph). In vitro ATRA can inhibit proliferation of myeloma cells by the downregulation of IL-6 receptors and/or its signal transducer glycoprotein 130 (gp130) surface expression on neoplastic cells, and by inhibition of IL-6 production by myelomatous and stromal cells (page 115, column 1, under ATRA in multiple myeloma). Expanding the spectrum of hematological malignancies, that may respond to ATRA remains a challenge, but several results show some activity of retinoids alone or in combination with other drugs in juvenile chronic myelogenous leukemia, myelodysplastic syndrome, cutaneous T-cell lymphoma and chronic myelogenous leukemia. Studies exploring the potential clinical synergim of ATRA-based combination therapies (e.g., with growth factors, other differentiating agents such as vitamin D3, immunomodulators like interferons or chemotherapeutic agents appear to be especially interesting (page 116, last paragraph).

The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because Sigmund et al. broadly teaches the use of a PDE 4 inhibitor, rolipram, for the treatment of a lymphoid malignancy. Although, roflumilast is not specifically disclosed by the reference, Reid teaches that that roflumilast is a PDE 4 inhibitor, which as described is more potent that rolipram. Further, Sacchi teaches the treatment of ATRA for various lymphoid malignancies.

Considering the teachings of Sigmund et al. who discloses the use of a PDE4 inhibitor for the treatment of a lymphoid malignancy, and also considering that it is well known in the art that roflumilast is a PDE4 inhibitor, but also that it is more potent than roflumilast and that

additionally ATRA is used for the treatment of various lymphoid malignancies, it would have been obvious to one of ordinary skill in the art to use roflumilast as the PDE4 inhibitor for the treatment of a lymphoid malignancy. Such a person would have been motivated to employ such roflumilast with a reasonable expectation to provide the same or similar therapeutic effects as rolipram disclosed by Reid and, further, because it is more potent than rolipram.

Further, one would have been motivated to additionally administer ATRA since it is also well known for the treatment of lymphoid malignancies. One of ordinary skill in the art would have been motivated to combine the teachings above since as combined would teach the invention as claimed. The idea of combining the administration of an agent known to be useful in the treatment of lymphoid malignancies flows logically from having been taught in the prior art.

Claims 39, 41-46, 75, 77 and 84 rejected under 35 U.S.C. 103(a) as being unpatentable over Sigmund et al (Leukemia (2001), provided by Applicant) and Reid (Current Opinion in Investigational Drugs, provided by Applicant) and Sacchi et al. (Hematological 1997; 82: 106-121) in view of Lerner et al. (Leukemia and Lymphoma, provided by Applicant) and Keeping (US 6,232,121).

Sigmund et al. teach of a lymphocytic leukemia which rolipram a specific inhibitor of phosphodiesterase (PDE) type 4, the PDE predominantly expressed in B-CLL cells, has been shown to induce cAMP-dependent apoptosis in these cells (abstract). In lymphoid cells, cytolysis induced by phosphodiesterase (PDE) inhibition results from an increase in protein kinase A-mediated phosphorylation of uknown lymphoid target proteins which eventually

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Lerner teaches that elevation of intracellular cAMP levels also induces apoptosis in a subset of normal and malignant lymphoid cells (page 40, column 1, first paragraph). Further, a distinguishing characteristic of PDE4 family is their involvement in heterologous desensitization to agents that increase cAMP (page 46, column 1, under PDE4).

Keeping teaches prostaglandin E2 as an agent to elevate intracellular cAMP (claims 8 and 9).

The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because Sigmund et al. broadly teaches the use of a PDE 4 inhibitor, rolipram, for the treatment of a lymphoid malignancy. Although, roflumilast is not specifically disclosed by the reference, Reid teaches that that roflumilast is a PDE 4 inhibitor, which as described is more potent that rolipram. Further, Sacchi teaches the treatment of ATRA for various lymphoid malignancies.

Considering the teachings of Sigmund et al. who discloses the use of a PDE4 inhibitor for the treatment of a lymphoid malignancy, and also considering that it is well known in the art that roflumilast is a PDE4 inhibitor, but also that it is more potent than roflumilast and that additionally ATRA is used for the treatment of various lymphoid malignancies, it would have been obvious to one of ordinary skill in the art to use roflumilast as the PDE4 inhibitor for the treatment of a lymphoid malignancy. Such a person would have been motivated to employ such roflumilast with a reasonable expectation to provide the same or similar therapeutic effects as rolipram disclosed by Reid and, further, because it is more potent than rolipram.

One would have been motivated to additionally administer ATRA since it is also well known for the treatment of lymphoid malignancies. One of ordinary skill in the art would have been motivated to combine the teachings above since as combined would teach the invention as claimed. The idea of combining the administration of an agent known to be useful in the treatment of lymphoid malignancies flows logically from having been taught in the prior art.

Further, given that PDE4 is known to increase cAMP which in turn is known to induce apoptosis, one would have been motivated to administer an additional agent such as prostaglandin E2 which is known to increase cAMP.

Conclusion

No claims are found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614